IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re Application of | : | 'COMPOUNDS' |
| HUGH CAIRNS et al | : | Group Art Unit 122 |
| Serial No 344,982 | : | David B Springer, Examiner |
| Filed 2 January 1982 | : | |

DECLARATION

I, DALE MICHAEL JACKSON, declare and say as follows:

I am a subject of the Queen of Great Britain and reside at 44 Hall Gate, Diseworth, Derbyshire, England.

I have obtained the degrees of Bachelor of Pharmacy (1967) and Doctor of Philosophy (Pharmacology) (1970) both from the University of Bath. I am also a Member of the Pharmaceutical Society and a Member of the British Pharmacological Society.

From 1970 to 1971 I was Tennovus Research Fellow in the Department of Anaesthetics at the University of Wales, Cardiff. Since 1971 I have worked in the Research and Development Laboratories of the Pharmaceutical Division of Fisons plc and currently hold the position of Principal Research Fellow in those laboratories.

The following test has been carried out under my supervision:-

MATERIALS AND METHODS

A Beagle dog is anaesthetised with pentobarbitone sodium 30 mg/kg i.v. and intubated using a cuffed endotracheal tube. A right and/or left saphenous vein is cannulated through the skin above the tarsal joint. An incision is then made on the inner aspect of the thigh. A branch of the femoral artery is exposed, cannulated with fine bore polythene tubing and the cannula connected to a blood pressure transducer. Records of phasic and mean arterial blood pressure and heart rate are made from the signal from the transducer. Pentobarbitone sodium (0.1 mg/kg/min) is then infused intravenously throughout the remainder of the experiment to maintain a constant level of anaesthesia.

A reproducible hypotensive response to sodium cromoglycate, given as a bolus injection, is then obtained. The dose is adjusted to give a submaximal fall in blood pressure of about 20-30 (± 3) mm Hg. An interval of 15 min between doses of sodium cromoglycate is allowed.

When a consistent response to sodium cromoglycate has been obtained, the compound under test is infused intravenously at a dose of 10 µg/kg/min (unless information is available to suggest a more appropriate infusion dose) for a 15 min period (ie between doses of sodium cromoglycate). 3M.

Following infusion of the test compound, the standard dose of sodium cromoglycate is repeated.

Compounds are tested at 10 µg/kg/min.

Following the termination of an experiment, the artery branch is tied off, the cannula removed and the wound sutured. The intravenous cannula is then withdrawn and the animal allowed to recover. The endotracheal tube is left in place until the dog removes it by coughing during recovery.

RESULTS

The results are shown in the following Table.

Table

| | A | B | C |
|---|---|---|---|
| | Disodium 4,6-dioxo -10-propyl-4H,6H-pyrano[3,2-g] quinoline-2,8-dicarboxylic acid | Disodium 4,6-dioxo -1-ethyl-10-propyl -4H,6H-pyrano [3,2-g]quinoline-2,8-dicarboxylic acid | Sodium 6,9-dihydro-6-methyl -9-oxo-2H-pyrano (2,3-g) quinoline -8-carboxylic acid |
| Degree of block | 100% | 100% | 0% |

INTERPRETATION AND SUMMARY

It is my experience that compounds which produce 100% block of the response to sodium cromoglycate are effective anti-allergy compounds in man.

The two compounds of Serial 344,982 would be regarded as good potential anti-allergic compounds. The Compound of Yamanouchi Japanese Patent Application No 073427 would be rejected as having no activity.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

This 24th day of January 1984

Declarant D. M. Jackson.

Post Office Address:

44 Hall Gate
Diseworth
Derbyshire
England

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